

Lloyd WOLFINBARGER
Appln. No.: 08/619,412

and page 6, line 25. New claims 73-75 have been added to further define the bone graft being processed. Support for new claims 73-75 is found in the present specification, for example at pages 1 and 2, and in the examples. No new matter has been added. Reexamination and reconsideration is respectfully requested.

- I. At page 2 of the Office Action, claims 59-72, have been rejected under the judicially created doctrine of obvious-type double patenting as being unpatentable over claims 1-58 of United States Patent No.: 5,556,379.***

The Examiner states that the subject matter claimed in the instant application is not patentably distinct from the claims of United States Patent No.: 5,556,379.

Applicant will file a terminal disclaimer in the present application upon the indication of allowable subject matter.

- II. At page 3 of the Office Action, claims 59-72 have been rejected under 35 U.S.C. § 103 as being unpatentable over Draenert (5,192,282) in view of Helenius.***

The Examiner contends that Draenert discloses a process of cleaning bone comprising the steps of selecting a bone and applying a vacuum to the bone in order to remove bone marrow.

The Examiner reasons that while Draenert does not disclose the use of a solution to solubilize the bone marrow, Draenert discloses the bone screw can also be used as a drug delivery system and that therefore, it is inherent that a solvent can also be applied to the bone grafts and that a process of removing bone marrow elements from the living bone of a patient to produce a substantially

Lloyd WOLFINBARGER
Appln. No.: 08/619,412

cell-free bone matrix is obviously achievable. The Examiner concludes that it would have been obvious to one of ordinary skill in the art to include the detergents disclosed in Helenius in the invention disclosed in Draenert in order to clean bone, since Draenert also discloses that the invention can be used as a delivery system.

In response to Applicants previously presented arguments, the Examiner states that Draenert is analogous art since it is reasonably pertinent to the particular problem being solved and thus can be relied upon as a basis for rejection of the claimed invention. The Examiner states that in the present case the Draenert patent is both within the Applicant's field of endeavor and is reasonably pertinent to the particular problem with which the Applicant is concerned. A brief analysis of Draenert is set forth below.

Draenert is directed to a surgical device and method. At lines 3 and 4 of the abstract, Draenert states "...use of...in arthroplastic *surgery*...as a drug delivery system." (Emphasis added). Draenert discloses that the bone screw is used during surgery to ensure that the *living* bone be filled with bone cement without endangering the *life* of the patient. In view of the following this rejection is respectfully traversed.

A. *Regarding the Examiner's contention, it is submitted that claims 59-72 are unobvious and patentable under 35 U.S.C. 103 over Draenert et al. in view of Helenius.*

1. *Applicants submit that the Examiner has failed to establish a prima facie case of obviousness.*

a. *Draenert is not analogous art; therefore Draenert can not be combined with other references to determine the patentability of the present claims.*

Applicants submit that Draenert is non-analogous prior art and is thus not relevant in determining obviousness. Whether a reference is considered analogous art is determined by a two-part test: (1) whether the art is from the same field of endeavor, regardless of the problem addressed and (2) if the reference is not within the field of the inventor's endeavor, whether the reference still is reasonably pertinent to the particular problem with which the inventor is involved.

Draenert's field of endeavor is clinical medicine, i.e. Draenert's field of endeavor is medical devices and surgical methods for use during surgery on a living patient. Again, please see Draenert, for example the abstract and examples. Applicant's field of endeavor is technical and does not involve living patients, i.e. Applicant's field of endeavor is the production of non-viable tissue grafts. All of Applicant's claims are directed to a bone "graft." The term "graft" is defined in Stedman's Medical Dictionary, 25th ed. ,Williams & Wilkins (1990), at page 666 a copy of which is enclosed herewith, as: "...Any free (unattached) tissue or organ for

Lloyd WOLFINBARGER
Appln. No.: 08/619,412

transplantation...;" the term "bone graft" is defined as: "bone transplanted from a donor site to a recipient site." Draenert is not in any way related to a bone *graft*.

Draenert is not reasonably pertinent to the problem being solved by the Applicant. Draenert discloses that his method and device solve the prior art problem of adequately anchoring a prosthesis into the boney bed of a *viable* bone in a *living* patient without adversely affecting the *life* of the patient. The present Applicant is concerned with solving the prior art problem of inadequately cleaned bone grafts harboring immunogenic and infectious material. Applicant's goal is to produce a *cell-free non-viable bone graft* free from contamination while Draenerts goal is to allow some bone marrow to drain in order to allow bone cement to enter and firmly anchor the *living bone* which bone is in a *living patient*. Please see the arguments presented on pages 6-11 of the preliminary amendment filed on October 21, 1996.

Applicant presented the above arguments to the Examiner in a preliminary amendment filed in the present application on October 21, 1996. In the present Office Action responsive to these arguments the Examiner simply states that: "....In this case, it is both." (both within Applicants field of endeavor and reasonably pertinent to the problem being solved). If this rejection is to be maintained, clarification from the Examiner is respectfully requested in the form of a full response to Applicants arguments.

Lloyd WOLFINBARGER
Appln. No.: 08/619,412

In view of the above, it is submitted that Draenert does not constitute analogous art and thus cannot be combined with other references to determine the patentability of Applicant's claims.

b. Assuming arguendo, Draenert is analogous art and that the combination of Draenert with Helenius proper, Applicant submits that the present claims are patentable and unobvious under 35 U.S.C. § 103 over Draenert in view of Helenius.

Claims 59-75 are directed to a process for cleaning essentially intact bone grafts. To establish a proper case of *prima facie* obviousness, the prior art as a whole must suggest the desirability of making the claimed combination and provide a reasonable expectation of success.

The present invention is directed to a process for cleaning *essentially intact* bone *grafts*. Draenert does not suggest any method or process using a bone *graft*. Again, the term "graft" is defined in Stedman's Medical Dictionary, 25th ed. ,Williams & Wilkins (1990), at page 666 a copy of which is enclosed herewith, as: "...Any free (unattached) tissue or organ for transplantation...;" bone graft is defined as: "bone transplanted from a donor site to a recipient site." Draenert does not suggest any process in any way related to a bone *graft*. Rather, Draenert discloses removing bone marrow from living bone *not* a bone graft so as to create a partial vacuum for drawing bone cement into the honeycombs of the bone to firmly anchor an implant in the bony bed during arthroplastic surgery on a *living* patient. The present invention

Lloyd WOLFINBARGER
Appln. No.: 08/619,412

requires subjecting a cadaveric essentially intact bone to negative pressure to remove the bone marrow elements.

Contrary to the Examiner's assertion that it would have been obvious to one of ordinary skill in the art at the time of the invention was made to include the detergents disclosed in Helenius and in the invention disclosed in Draenert in order to clean bone, Draenert does not teach or suggest delivering a detergent to or from the interior of a bone. In fact, Draenert *teaches away* from delivering a detergent to or from the interior of the bone, since such delivery would result in cell lyses which is hazardous to the life of the patient. Draenert is directed exclusively to an *in-vivo, clinical* method. Helenius is directed to the solubilization of membranes by detergents in *in-vitro* systems. It is well know to those of ordinary skill in the art that a detergent lyses cell membranes and is thus detrimental to a living system. Further, Helenius does not teach or suggest the use of detergents in an *in-vivo* system to any clean body tissue let alone cadaveric bone.

In the present case, Draenert *requires that the method result in a living patient* having a firmly anchored prosthesis. Draenert does not suggest using negative or vacuum pressure to pull solvent through a bone graft thereby solubilizing the bone marrow, and allowing the solvent and solubilized bone marrow to exit the bone, thus achieving a cleaned bone graft, as required by the

Lloyd WOLFINBARGER
Appln. No.: 08/619,412

present claims. Draenert does not suggest cleaning bone marrow from the bone. Rather, Draenert suggests removing an amount of bone marrow, and creating a partial vacuum within the bone. Draenert does not suggest cleaning bone, let alone cleaning bone by delivering a detergent to the interior of the bone, since such delivery would result in cell lyses (cell death) and could result in the death of the patient. The combination of Draenert with Helenius does not provide a reasonable expectation of success, since cleaning a bone using the detergent of Helenius to produce a cell-free matrix would result in patient death. Draenert teaches away from cell lyses since Draenert requires a living patient.

In conclusion, Draenert does not teach or suggest a process for cleaning a bone graft, or a process requiring subjecting the bone to a negative pressure to remove the bone marrow. Further, Helenius does not overcome the deficiencies of Draenert, since Helenius also does not teach or suggest a bone graft (a bone free of other tissue), or subjecting a bone graft to a negative pressure to remove bone marrow elements, as required by the present claims.

Regarding claim 59-66, claims 59-66 all require applying a vacuum to an essentially intact bone to draw a solvent through the essentially intact bone to solubilize the bone marrow. Draenert teaches using a bone screw to allow an amount of bone marrow to drain with suction assistance, thus creating a partial vacuum which vacuum draws an amount of bone cement into

Lloyd WOLFINBARGER
Appln. No.: 08/619,412

the bone or a drug into the bone. The present claims require that the solvent be drawn *through*, that is, into and out of, the bone. As the solvent is drawn through the bone it solubilizes the bone marrow and the solvent and any solubilized bone marrow is carried through and out of the bone to achieve the goal of producing a cleaned bone graft. Draenert discloses *only the delivery* of a bone cement or a drug to the interior of a living bone, *where the cement or drug remain in the living bone* of the living patient. Draenert teaches the removal of a small amount of bone marrow from a living bone, by *drainage*. Draenert does not suggest removing bone marrow by applying vacuum to draw a solvent along with solubilized bone marrow through and out of the bone. Draenert creates a partial vacuum in the bone via suction assisted drainage and then uses this partial vacuum to *introduce* substances into the bone; Draenert does not in any way suggest: (i) a bone *graft* (a bone free from other tissue); or (ii) using a vacuum or negative pressure mediated *flow* of solvent to remove elements from the bone; as required by the present claims. The Examiner is requested to respond to this argument.

Regarding claims 67-69, claims 67-69 *require* subjecting the bone marrow to a negative-pressure *flow* of solvent. Again, Draenert does not teach or suggest subjecting the bone marrow of a patient to a pressurized flow of anything let alone a negative pressure-mediated flow of solvent, as required by the present claims. The term "flow" is defined in Stedman's Medical Dictionary, 25th ed. ,Williams & Wilkins (1990), at page 597 a copy of which is enclosed

Lloyd WOLFINBARGER
Appln. No.: 08/619,412

herewith, as: "...Movement of a fluid....specifically the volume of fluid...passing a given point per unit of time..." Draenert does not teach or suggest subjecting a living or non-viable bone to a flow of any kind. In fact Draenert *teaches away* from subjecting a living bone to a "flow" since in order for Draenert to solve the problem of adequately anchoring a bone it is essential that the bone cement be introduced into and remain in the bone without movement (flow) through the bone. Further, Draenert does not suggest an isolated bone free from other tissue as required by the present claims (i.e. the term "bone graft").

Regarding claim 70, claim 70 also requires inducing a negative pressure-mediated flow of solvent through the bone. Accordingly, please see the arguments presented above regarding claims 67-69. Draenert does not suggest inducing a "flow" of any kind, let alone inducing a negative pressure-mediated flow of solvent through the bone as required by present claim 70.

Regarding claims 71 and 72, claims 71 and 72, require subjecting the bone marrow of an essentially intact bone graft to negative pressure to accomplish the removal of such bone marrow. Claim 71 requires that substantially all of the bone marrow be removed, and claim 72 requires the production of a cell-free matrix. Draenert does not suggest subjecting a bone *graft* to anything. Draenert does not suggest subjecting bone marrow from a bone graft to negative pressure under conditions effective to remove the substantially all of the bone marrow to produce

Lloyd WOLFINBARGER
Appln. No.: 08/619,412

a cell-free matrix, as required by present claims 71 and 72. Draenert teaches the removal of only an amount of bone marrow sufficient to allow the bone cement to be drawn into the bone.

Draenert does not teach or suggest removing bone marrow from the cancellous bone space at all.

Claims 73-75 further define the “essentially intact bone graft” as being for example, at least one-third or at least one-half of an intact bone. Claims 73-75 are either directly or indirectly dependent on the above rejected claims. Draenert does not suggest these claims since Draenert does not suggest subjecting a bone or bone marrow to negative pressure which subjecting results in the removal of bone marrow from the bone, as required by all of the present claims. Further, Draenert does not suggest any method or process using a bone graft, let alone the specific grafts claimed in present claims 73-75. Again, the term “graft” is defined as: “...Any free (unattached) tissue or organ for transplantation...;” bone graft is defined as: “bone transplanted from a donor site to a recipient site.” Draenert does not suggest any process in any way related to a bone *graft*.

In view of the above, Applicant asserts that Draenert constitutes non-analogous art. Assuming *arguendo*, Draenert constitutes analogous art and that the combination of Draenert with Helenius proper, it is submitted that the Examiner has not established a proper *prima facie* case of obviousness. It is submitted that neither Draenert nor Helenius, taken alone or together,

Lloyd WOLFINBARGER
Appln. No.: 08/619,412

suggest the present invention as claimed in claims 59-75. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

III. At page 4 of the Office Action, claims 59-72 have been rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over applicant's admission of the prior art disclosed in the Background of the Invention.

The Examiner states that Applicant admits that it is well known to clean smaller bones and that the term "large" is relative. The Examiner concludes that it would have been obvious that the effectiveness of the cleaning process is largely dependent of the expertised physician and whether or not a physician chooses to include agitation or not. In view of the following, this rejection is respectfully traversed.

It appears that the Examiner is contending that the Background of the Invention section of the present application anticipates all of the claims or renders all of them obvious. Regarding anticipation, anticipation requires that each and every element of the claimed invention be disclosed in a single prior art reference, in this case the Background of the Invention section of the present application. In view of the following, this rejection is respectfully traversed.

The Examiner states that Applicant at page 1 of the specification admits that the term "large" is relative. Applicant nowhere on page 1 states that the term "large" is relative. In fact,

Lloyd WOLFINBARGER
Appln. No.: 08/619,412

Applicant defines "large" throughout the specification as an essentially intact bone graft which is a substantial part of a whole or intact bone. At page 1, Applicant states that such a graft includes the size range of whole bones down to bone pieces as small as one-half to one-third of a whole bone. The specification and examples discuss that such bone grafts include a proximal or distal femur, femur head, etc.

The present invention is not directed to cleaning small bone grafts. The definition of the term "small bone graft" is well known to those of ordinary skill in the art. This term means small bone grafts which of course are smaller than Applicant's definition of a large bone graft, and such small bone grafts are known in the industry as "cut" bone grafts and include for example, cancellous cubes, iliac crest wedges, cloward dowels, bone chips and bone shavings. In the Background of the Invention section, Applicant discusses the cleaning of such small bone grafts at page 2, as including soaking, sonication, and/or lavage. At page 3 of the specification Applicant states that "Current processing techniques do not effectively remove bone marrow from the less solvent-accessible cancellous bone spaces within the bone grafts (large)...the femoral head area of the proximal femur, because current processing techniques rely upon soaking procedures which may or may not include agitation." Applicant is not stating that agitation will remove bone marrow; rather, Applicant relates that soaking with or without agitation does not result in the removal of bone marrow from the cancellous bone spaces of a

Lloyd WOLFINBARGER
Appln. No.: 08/619,412

large bone graft. The Examiner states that "...cleaning process...the expertised physician...a physician chooses..." In the present industry it is not a "physician" who processes bone grafts. Rather, the bone grafts are cleaned and processed by technicians under strict guidelines. Bone grafts are not processed in a clinical setting. Cleaned and processed bone grafts are provided to physicians for surgical implantation into a living patient.

At page 3 and 4, Applicant discusses the VIP process and states that this process includes surface disinfection, cleaning and removal of debris from the cut pieces with a surfactant at elevated temperatures, and terminal disinfection. Applicant states that the VIP process is used to clean the *surfaces* of large bone grafts, and to remove bone marrow from the cancellous bone spaces of small bone grafts cut from the larger grafts. That is, in the VIP process the surface of a large bone graft is cleaned, the large bone graft is cut into small bone grafts exposing the cancellous bone making the bone marrow more accessible, and these small cut bone grafts are cleaned according to the process..

Applicant in the "Background of the Invention" section does not admit that the term "large" is relative; rather, Applicant clearly defines what is meant by the term "large." The claims have been amended to replace the term "large" with the term "essentially intact" to more clearly define the bone graft being processed. Applicant in the Background of the Invention

Lloyd WOLFINBARGER
Appln. No.: 08/619,412

section of the present application does not admit that the prior art techniques are similar to the presently claimed techniques. The present claims all require subjecting the essentially intact bone graft to negative pressure, or a negative or vacuum pressure mediated flow of solvent. This negative pressure mediated flow of solvent is not disclosed or suggested in the Background of the Invention section of the present application. In view of the above, it is submitted that nothing in the Background of the Invention section of the present application anticipates or renders the present invention obvious within the meaning of 35 U.S.C. § 102 or § 103, respectively. Accordingly the Examiner is respectfully requested to withdraw this rejection.

IV. At page 5 of the Office Action, claims 59-72, have been rejected under 35 U.S.C. § 103(a) as being obvious over Skrinnyuk in view of Morse et. al. (5,513,662).

The Examiner contends that both of these references disclose a method of removing bone marrow via a mechanical means such as a vacuum. The Examiner states that Skrinnyuk discloses extracting bone marrow cells and preserving solutions from spongy bone transplant material by vacuum, but does not disclose a method of contacting a bone internal matrix with a solution. The Examiner states that '662 disclose a process of cleaning bone by introducing a detergent. The Examiner concludes that it would have been obvious to one having ordinary skill in the art of Skrinnyuk to apply a detergent to clean a bone. In view of the following, this rejection is respectfully traversed.

Lloyd WOLFINBARGER
Appln. No.: 08/619,412

It is submitted that '662 does not constitute proper prior art against the claims of the present invention since '662 is not entitled to rely on the filing date of its parent application U.S. Patent No.:5,333,626 (first filed on December 31, 1991), since none of the material relating to negative or vacuum pressure added in the CIP application ('662) finds support under 35 U.S.C. § 112 in the parent application '626. Accordingly, '662 is only entitled to its filing date of January 21, 1994, as to the newly added material. Applicant's effective filing date for the present application is the filing date of the first filed application, August 19, 1994 for U.S. Serial No.:293,206, now abandoned which is the parent application of U.S. Patent No.:5,556,379, of which the present application is a division thereof. Filed herewith, please find a declaration under 37 C.F.R. Rule 1.131(a) establishing Applicant's prior invention. In view of the foregoing and the declaration, it is submitted that Morse et. al. '662 does not constitute proper prior art against the claims of the present application.

Skrinnyuk is directed to cleaning *only small bone grafts from spongy bone*. Skrinnyuk at pages 1 and 2, states that bone marrow cells are extracted from "spongy" bone (see the title, text page 1, line 3; page 2, lines 4, 7, 10, 14 and 18, and the claim at page 3.). Skrinnyuk in order to clean spongy bone (page 2, paragraph 5) separates the spongy bone from the tibia in the form of shavings. Skrinnyuk discloses placing bone shavings in a vessel with a physiological solution

Lloyd WOLFINBARGER
Appln. No.: 08/619,412

(saline) and drawing a vacuum to facilitate removal of any remaining preservative solution and cells.

Skrinnyuk does not teach or suggest producing an essentially intact bone graft as required by the present claims. Skrinnyuk does not teach or suggest subjecting such an essentially intact bone graft to a negative pressure-mediated flow of solvent to remove bone marrow, nor does he suggest subjecting the intact bone to negative pressure under conditions effective to remove bone marrow, as required by the present claims.

Assuming *arguendo* Morse et. al. '662 proper prior art, '662 does not cure the deficiencies of Skrinnyuk, since '662 also does not teach or suggest subjecting the bone to a negative pressure to produce a cell-free matrix, or to a negative or vacuum pressure-mediated flow of solvent.

In view of the above and the submitted Declaration, it is submitted that '662 does not constitute proper prior art against the claims of the present application, and assuming *arguendo* that '662 is proper prior art nothing in Skrinnyuk or '662 taken alone or together render the claimed invention obvious within the meaning of 35 U.S.C. § 103. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

Lloyd WOLFINBARGER
Appln. No.: 08/619,412

It is submitted that claims 59-75 are in condition for immediate allowance and early notice to that effect is respectfully requested. The Examiner is invited to contact the undersigned at her Reston, Virginia telephone number on any questions that may arise.

Respectfully submitted,
JONES & VOLENTINE



Susanne M. Hopkins
Attorney for Applicant
Registration No. 33,247

Date: January 16, 1998

JONES & VOLENTINE
12200 Sunrise Valley Drive
Suite 150
Reston, Virginia 20191
(703)715-0870